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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Björck *et al.*	Examiner:	Nita M. Minnifield
Serial No.:	08/325,278	Group Art Unit:	1645
Filed:	April 28, 1993		
For:	*"Protein L and Hybrid Proteins Thereof"*		
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Commissioner for Patents
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Considered 7/8/04 MMM

DECLARATION OF DR. HALLDIS HELLEBUST

Sir

I, Halldis Hellebust, declare as follows:

1. I submit this declaration in support of the accompanying Response to Final Office Action.
2. I make this declaration based upon my training, knowledge, education and experience in the field of protein engineering, protein expression, protein analysis, protein purification, my review of the above referenced patent application, the history of

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prosecution of this application, and my review of the Office Action dated September 10, 2003 that issued in connection with the above-referenced patent application, as well as the art cited in that Office Action: Kastern *et al.* (Infection and Immunity, 1990, vol. 58, p1217-1222.)

3. I am familiar with the technology of Kastern (1990) and understand the teachings expressed therein.

4. I hold the degree of a Master of Science in biochemical engineering from the Norwegian Institute of Technology, Trondheim, and a PhD in biotechnology from the Royal Institute of Technology, Stockholm

5. I have over 20 years work experience in the field of protein biochemistry. A significant part of this work was done on Protein A and Protein G which are other proteins used for purification of antibodies.

6. I am an employee of Affitech A/S who are the assignees of the above application and hold the position of Director for Discovery and Production. I have been working with protein L for three years and I am familiar with all the aspects of its biology. I started working on Protein L as Senior Scientist in 2000. My work has included design of a vector suitable for production of Protein L in a fermenter, establishing the fermentation protocol, purification of the produced Protein L and coupling Protein L to matrices useful in using Protein L for purification of antibodies. As Director for Discovery and Production, I am now responsible for all aspects of Protein L related to its science and production.

7. Based on my reading of the office action, which was mailed September 10, 2003, I understand that the Examiner considers that a protein having the ability to bind to the light chains of immunoglobulins as defined in claim 14 is disclosed by Kastern *et al.* (1990). I respectfully disagree.

8. Kastern *et al.*, (1990) relates to the characterisation of protein L, which is an immunoglobulin light chain binding-protein expressed on the surface of certain strains of *P magnus*. In particular, this paper does disclose the N-terminal sequence of two polypeptide fragments of protein L (see Figure 3, p1220). A seven amino acid long sequence from one of these was used to design oligonucleotide probes (shown in Figure 4, p1220), which were in turn used to clone a sequence of 220 nucleotides (shown in Figure 5, p1220). A corresponding amino acid sequence was derived and is also shown in Figure 5. This is described under the heading "cloning and sequence

added). Kastern *et al.*, (1990) does not disclose the cloning of the complete protein L gene. The cloning of the complete protein L gene was only achieved subsequently (Kastern *et al* J. Biological Chemistry, 1992, vol. 267, pp.12820-12825). The complete sequence of the protein L gene and corresponding amino acid sequence of some 719 amino acids is shown in Figure 1 of Kastern *et al.* (1992). That sequence is not disclosed either explicitly or implicitly in Kastern *et al.* (1990).

9. Kastern *et al* (1990) does disclose a sequence of 220 nucleotides, which is a small fragment of the complete protein L gene. This sequence corresponds to positions 109 to 182 of SEQ ID NO: 1 given in the present application. It corresponds to a part of the sequence identified as the B2 domain (positions 81-152 of SEQ ID NO:1) and of the B3 domain (positions 153-224 of SEQ ID NO:1). However, the sequence does not include in their entirety any of the immunoglobulin binding domains B1-B4 identified in the application. It omits the first 28 amino acids of domain B2 and last 42 amino acids of B3. These deletions are substantial and would compromise the functionality of such a sequence. The sequence described in Kastern *et al.* (1990) does not therefore correspond to any of the binding domains B1-B4 identified in the application and would not be expected to bind the light chain of immunoglobulins.

10. The Examiner has referred at page 2, final paragraph of the office action to "Sequence Search Result #2" as disclosing a 99.7% match with SEQ ID NO:1 and that it is set forth in the publication of Kastern *et al.* (1990). The Examiner has also referred on page 3, final paragraph to additional search results on the individual domains B1-B4 concluding these are also disclosed. I would emphasise that such sequences were not disclosed in the Kastern *et al.* (1990). The complete sequence of protein L and the individual sequence of the binding domains B1-B4 were only identified in the subsequent Kastern *et al.* (1992). That later paper does identify the individual binding domains. However, such information cannot be derived in any way from the earlier Kastern *et al.* (1990) disclosure. It is not clear to me on what basis the Examiner has reached the conclusion that these sequences are disclosed in the earlier paper though I do note that the Sequence Search Results refer to both Kastern *et al.* (1990) and the subsequently published reference Kastern *et al.* (1992), which is identified in the search result as "Bjöerck Sjoebring & Kastern, J. Biol. Chem. 267:12820-12825

the reference does not disclose amino acids 1 to 305 of SEQ ID NO 1. Nor does it disclose the amino acids 5 to 80 of SEQ ID NO 1 corresponding to the B1 domain, amino acids 81 to 152 of SEQ ID NO I corresponding to the B2 domain, amino acids 153 to 224 of SEQ ID NO 1 corresponding to the B3 domain, or amino acids 225 to 296 of SEQ ID NO 1 corresponding to the B4 domain.

11. Finally, I understand that the Examiner has argued in the section bridging pages 3-4 of the office action that Kastern *et al.* (1990) discloses a hybrid protein consisting essentially of one or more of the B1-B4 domains and domains which bind to heavy chains of immunoglobulin G as defined in claim 15. There is however absolutely no disclosure in Kastern *et al* (1990) of such a fusion protein comprising domains of protein L which bind to the light chain of immunoglobulins and domains which bind to the heavy chains of immunoglobulin G. Such a construct including both the binding domains identified in the invention and additional elements which bind to heavy chains is in no way suggested by Kastern *et al.* (1990).

12. It is therefore my considered opinion that Kastern *et al.* (1990) does not disclose or suggest a protein consisting essentially of any of the amino acid sequence of SEQ ID NO:1 or a protein consisting essentially of the binding domains B1-B4 or a multiple of such domains. It further does not disclose or suggest a hybrid protein incorporating one or more of the B1-B4 domains and domains which bind to the heavy chain of immunoglobulin G. Correspondingly, it does not describe a reagent kit comprising any such protein in combination with a detection reagent.

All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further these statements are made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such wilful false statements may jeopardise the validity of this Declaration, the patent application, or any patents issuing thereon.

Declared 3rd of February 2004. Hallis Hellsten